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A review of randomised controlled trials comparing ultrasound-guided foam sclerotherapy with endothermal ablation for the treatment of great saphenous varicose veins

Huw OB Davies¹, Matthew Popplewell¹, Katy Darvall², Gareth Bate¹ and Andrew W Bradbury¹

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Abstract

Objective: The last 10 years have seen the introduction into everyday clinical practice of a wide range of novel non-surgical treatments for varicose veins. In July 2013, the UK National Institute for Health and Care Excellence recommended the following treatment hierarchy for varicose veins: endothermal ablation, ultrasound-guided foam sclerotherapy, surgery and compression hosiery. The aim of this paper is to review the randomised controlled trials that have compared endothermal ablation and ultrasound-guided foam sclerotherapy to determine if the level I evidence base still supports an “endothermal ablation first” strategy for the treatment of varicose veins.

Methods: A PubMed and OVID literature search (until 31 January 2015) was performed and randomised controlled trials comparing endothermal ablation and ultrasound-guided foam sclerotherapy were obtained.

Results: Although anatomical success appeared higher with endothermal ablation than ultrasound-guided foam sclerotherapy, clinical success and patient-reported outcomes measures were similar. Morbidity and complication rates were very low and not significantly different between endothermal ablation and ultrasound-guided foam sclerotherapy. Ultrasound-guided foam sclerotherapy was consistently less expensive than endothermal ablation.

Conclusions: All endovenous modalities appear to be successful and have a role in modern day practice. Although further work is required to optimise ultrasound-guided foam sclerotherapy technique to maximise anatomical success and minimise retreatment, the present level I evidence base shows there is no significant difference in clinically important outcomes between ultrasound-guided foam sclerotherapy and endothermal ablation. As ultrasound-guided foam sclerotherapy is less expensive, it is likely to be a more cost-effective option in most patients in most healthcare settings. Strict adherence to the treatment hierarchy recommended by National Institute for Health and Care Excellence seems unjustified.

Keywords

Varicose veins, endovenous technique, foam sclerotherapy, endovenous thermal ablation, randomised controlled trial

Introduction

For almost 100 years, surgery was the only available treatment for varicose veins (VV). However, over the last 10 years a wide range of novel non-surgical, local and tumescent anaesthetic, treatment modalities have been described, evaluated and entered clinical practice around the world.

In July 2013, the UK National Institute for Health and Care Excellence (NICE) recommended (Clinical Guideline, CG, 168) the following treatment hierarchy for VV: endothermal ablation (ETA), ultrasound-guided foam sclerotherapy (UGFS), surgery and

compression hosiery.¹ This hierarchy was supported in the Vascular Society of Great Britain and Ireland (VSGBI) and Royal College of Surgeons (RCS) Commissioning Guide published in December 2013²

¹Department of Vascular Surgery, University of Birmingham, Solihull Hospital, Birmingham, UK

²North Devon District Hospital, Barnstaple, Devon, UK

Corresponding author:

Huw Davies, Department of Vascular Surgery, University of Birmingham, Solihull Hospital, Netherwood House, Birmingham B91 2JL, UK.
Email: huw.davies@heartofengland.nhs.uk

Table 1. Comparison of RCT allocated treatments.

Trial	Legs randomised				Total
	EVLA	RFA	UGFS	CS	
Rasmussen	144	148	125 (124 received treatment)	125 (124 received treatment)	580
Lattimer	50 (4 lost to follow-up)	–	50 (5 lost to follow-up)	–	100
Biemans	80 (2 procedure failed)	–	80 (1 lost to follow up, 2 other intervention)	80 (3 procedure failed, 4 other intervention, 8 no intervention)	240
Brittenden	292	–	212 (183 completed follow up)	294 (236 completed follow up) (251 completed follow up)	798

RCT: randomised controlled trials; EVLA: endovenous laser ablation; RFA: radiofrequency ablation; UGFS: ultrasound-guided foam sclerotherapy; CS: conventional surgery.

and by the NICE Quality Standards (QS 67) which was published in August 2014.³

Despite this, conventional surgery is still frequently offered to VV patients being treated within the UK National Health Service⁴ and there is considerable continuing uncertainty regarding the clinical and cost-effectiveness of surgery, ETA and UGFS.⁵

The aim of this paper is to review the randomised controlled trials (RCTs) that have compared ETA, using either radiofrequency (RFA) or endovenous laser ablation (EVLA), and UGFS to determine if the level 1 evidence base still supports an “ETA first” strategy for the treatment of VV.

Methods

Search strategy

PubMed and OVID literature searches were performed until 31 January 2015 using the terms RCT, sclerotherapy, radiofrequency ablation, laser ablation, endovenous and endothermal linked with varicose veins. Abstracts were screened and the full papers obtained if they compared UGFS with ETA for the treatment of VV.

Inclusion/exclusion criteria

Papers were included within the review if they were classified as randomised controlled trials; all other study types were excluded.

Analysis

ETA and UGFS RCT data were analysed in terms of endovenous methodology, technical success, clinical

success, morbidity, complication rates, costs and time to return to work.

Results

RCTs identified

Four RCTs, six publications, were identified (Rasmussen et al.,^{6,7} Lattimer et al.,^{8,9} Biemans et al.¹⁰ and Brittenden et al.¹¹), all of which studied only great saphenous (GSV) VV (only Rasmussen allowed recurrent GSV VV, provided the GSV was still present in the groin). Two papers described initial results^{6,8} and were followed by further publications reporting longer-term outcomes.^{7,9} Rasmussen compared EVLA, RFA, UGFS and conventional surgery (CS) in 580 legs, Lattimer compared EVLA and UGFS in 100 legs, Biemans compared EVLA, UGFS and CS in 240 legs, and Brittenden compared EVLA, UGFS and CS in 798 legs (Table 1).

Comparison of endovenous techniques utilised (Table 2)

Brittenden's multi-centre trial did not specify laser manufacturer, wavelength or fibre type presumably as these varied across hospitals. All of the other RCTs use bare-tipped fibres and lasers of varying wavelength: Rasmussen 980 and 1470 nm (Ceralas D, Biolitec, Jena Germany); Lattimer 1470 nm (ELVeS Painless diode laser, Biolitec Inc, East Long Meadow, MA, 01028, USA); Biemans 940 nm (manufacturer not specified). For most treatments, the laser fibre appears to have been inserted into the GSV under ultrasound-guidance at approximately the level of the knee, or at

Table 2. Comparison of treatment techniques.

Intervention		Study			
		Rasmussen	Lattimer	Biemans	Brittenden
EVLA	Fibre	Bare tipped 980–1470 nm (Ceralas D)	Bare tipped 1470 nm (ELVeS)	Bare tipped 940 nm (manufacturer not specified)	No specification
	Cannulation	All studies – GSV under ultrasound guidance at level of knee or lowest point of reflux, advanced to 2 cm from SFJ			
	Energy	69 J/cm	69 J/cm	>60 J/cm	>70 J/cm
	Anaesthesia	All studies – tumescence analgesia +/- light sedation			
RFA	Tributaries	Concurrent phlebectomies	Concurrent phlebectomies	Concurrent or delayed (3 months) phlebectomies	UGFS at 6 weeks (1 centre concurrent phlebectomies)
		VNUS, cannulation just below knee GSV or lowest point of reflux with concurrent phlebectomies, under tumescence analgesia	–	–	–
UGFS	Sclerosant	Polidocanol	Sodium tetradecyl sulphate	Polidocanol	Sodium tetradecyl sulphate
	Concentration	3%	1%	3%	3% truncal, 1% to varicosities
	Volume	Not specified	Median 12 ml/session	Maximum 10 ml/session	Maximum 12 ml/session
	Technique	Single cannula just below knee. Continue injection until foam visualised at SFJ and GSV contracted	Single cannula at knee level. If GSV ≥ 8 mm then tumescence to reduce diameter	As per 2nd European Consensus	No specifications regarding number of injections/sites

EVLA: endovenous laser ablation; RFA: radiofrequency ablation; UGFS: ultrasound-guided foam sclerotherapy; SFJ: sapheno-femoral junction; GSV: great saphenous veins

the level of lowest incompetence in the thigh. The laser fibre tip was then advanced to within 2 cm of the sapheno-femoral junction (SFJ) after which the GSV was ablated by slow withdrawal of the catheter. Rasmussen achieved a median of 69 J/cm, Lattimer delivered a median of 69 J/cm, Biemans aimed for at least 60 J/cm and Brittenden's study aimed for at least 70 J/cm energy delivery. This was in concordance with previous work suggesting that at least 60 J/cm energy delivery is required for satisfactory vein closure.¹² All of the RCTs used tumescence anaesthesia and some patients received light sedation. Rasmussen et al.⁶ and Lattimer et al.⁸ performed EVLA with concurrent phlebectomies; Biemans et al.¹⁰ with either concurrent or delayed (three months) phlebectomies; and Brittenden et al.¹¹ with UGFS to tributaries at six weeks (except one site that performed concurrent phlebectomies).¹³

Only Rasmussen evaluated RFA and used a VNUS ClosureFAST catheter (Covidien, Mansfield, Mass, USA) inserted under ultrasound-guidance into the GSV just below the knee or at the lowest point of reflux in the thigh. This was performed using tumescent anaesthesia with light sedation and tributaries were removed with concurrent phlebectomies.⁶

UGFS techniques varied considerably. Rasmussen inserted a single cannula into the GSV just below the knee and injected 3% polidocanol foam (volume not specified) until the foam was visualised by ultrasound at the SFJ and the GSV was contracted (in spasm) throughout its length.⁶ Lattimer inserted a single cannula into the GSV at knee level and injected 1% sodium tetradecyl sulphate (STS) using a median of 12 ml/session. If the GSV was ≥ 8 mm in diameter, tumescence anaesthesia was used to compress the vein before introduction of STS foam. Lattimer performed further foam treatments in 4.6% of patients who initially received EVLA and in 56% of the patients who had been randomised to foam. Biemans performed UGFS as per the Second European Consensus¹⁴ using 3% polidocanol (with a maximum of 10 ml/session). Six patients (4.6%) in the UGFS group had further foam treatment in the first six months. Brittenden did not provide information on use of cannulas (numbers and sites) but stipulated that 3% STS be used on truncal veins and 1% STS on varicosities,¹³ with a maximum of 12 ml/session. At six weeks, 38% UGFS and 31% EVLA patients underwent a further UGFS treatment. All trials used foam volumes in accordance with manufacturers' licences.

For RCTs including CS, SFJ ligation was performed and the GSV stripped to the knee, or just below, with concurrent phlebectomies. Rasmussen performed CS using tumescence anaesthesia under light sedation; Biemans used general anaesthetic; and Brittenden did not specify the type of anaesthesia.

Technical success

Rasmussen defined technical success as a closed or absent GSV without reflux, and failure as an open segment of GSV > 10 cm in length or GSV unsuccessfully stripped. Five GSVs were open after one month in the UGFS group and these were re-treated. At one year, the technical failure rates were 16.3% for UGFS, 5.8% for EVLA and 4.8% for RFA ($p < 0.001$, χ^2);⁶ and at three years they were 26.4% for UGFS, 6.8% for EVLA and 7% RFA ($p < 0.0001$, statistical test not stated).⁷

Lattimer defined technical success as complete ablation of GSV reflux (occlusion not required) and failure as reflux anywhere in the above knee GSV. At three months, the technical success rate (as defined by absence of above knee GSV reflux on duplex) was 80% in both the EVLA and UGFS groups; and at 15 months, global absence of reflux was 41% for EVLA and 43% for UGFS. However, at 15 months, complete GSV occlusion was observed in 95.5% of the EVLA, and 67.4% of the UGFS, patients ($p < 0.001$, Fisher exact test) at 15 months.

Biemans defined technical success as complete obliteration of, without flow or reflux in, the mid-thigh GSV. At 12 months, the technical success rate was 88.5% for EVLA and 72.7% for UGFS ($p < 0.001$, χ^2).

Brittenden defined technical success according to Kundu et al.¹⁵ as 'successful ablation of the target vein as demonstrated by a complete lack of flow or disappearance of vein by duplex ultrasound imaging in the entire treated segment.' At six weeks, the technical success rate was 83% for EVLA and 54.6% for UGFS ($p \leq 0.01$, statistical test not stated).

Clinical success

Rasmussen reported clinical success using the Venous Clinical Severity Score (VCSS),¹⁶ Aberdeen Varicose Vein Questionnaire (AVVQ),¹⁷ Short Form-36 (SF-36[®]) (QualityMetric, Lincoln, Rhode Island, USA) and visual analogue scores (VAS) for pain. All three improved significantly in all four patients groups and there was no difference between EVLA, RFA, UGFS and CS at one or three years.

Lattimer reported clinical success using the VCSS, AVVQ and the Saphenous Treatment Score¹⁸. All three improved significantly in both groups and there was no difference between EVLA and UGFS out to 15 months; although seven-day pain scores were significantly higher with EVLA.

Biemans reported clinical success using the chronic venous insufficiency quality of life (QoL) questionnaire (CIVIQ)¹⁹ and EuroQoL 5D (EQ-5D) (EuroQol, Rotterdam, Netherlands). These both improved at three months and there was no difference between EVLA and UGFS out to one year.

Brittenden reported clinical success using AVVQ, VCSS, EQ-5D, SF-36 and clinical vein appearance. At six months both EVLA and UGFS showed improvement in AVVQ and VCSS, with no statistical difference between EVLA and UGFS reported. Both EQ-5D and the physical component of SF-36 showed improvement in all groups, with no statistical difference between groups. The SF-36 mental component was slightly better in EVLA vs. UGFS (p 0.048, using general linear model with adjustments for covariates used in minimisation algorithm) and all groups improved. Patient and nurses reported no difference between UGFS and EVLA in terms of residual veins at six weeks, but fewer residual veins were reported by patients (not by nurses) in EVLA compared to UGFS at six months.

Morbidity and complication rates

Morbidity and complication rates were very low in all RCTs in all treatment groups. Rasmussen reported one iliac vein thrombosis with pulmonary embolus one week after UGFS. Lattimer reported no serious complications except one EVLA patient who developed a common femoral vein thrombosis. Biemans noted a low frequency of minor morbidity (such as hyperpigmentation, thrombophlebitis and paraesthesia), which was not statistically significant between groups. Brittenden reported no difference between groups in terms of serious adverse events (these included deep vein thrombosis and pain).

Costs and return to work

Only Rasmussen, Lattimer and Brittenden (reported by Tassie et al.²⁰) looked at these outcomes. Rasmussen reported a quicker return to work after UGFS and RFA when compared to EVLA. Treatment costs were €994 for UGFS, €1360 EVLA and €1436 RFA (cost of catheter higher than for EVLA). If time lost from work is included overall costs were €1554 UGFS, €2200 EVLA and €1996 RFA. Lattimer also found a cost advantage with UGFS (£230.24) compared to EVLA (£724.72), even if further foam treatments were required. Brittenden's trial demonstrated treatment costs of £245 for UGFS and £737 for EVLA (the difference appears to partly be due to increased consumable costs). At six months total health service costs (including follow up and unplanned use of health service), UGFS costs were £465 and EVLA were £975.

Discussion

Although there are a large number of observational studies available in the literature, randomised data

comparing ETA with UGFS remains limited. Furthermore, there are important differences between the RCTs in terms of the:

1. Technology and techniques used for ablating the GSV as well the tributaries and varices themselves.
2. Definitions of technical and clinical success and failure.
3. Limited duration and completeness of follow.
4. Variable estimates of cost.

It is therefore difficult to draw any firm conclusions regarding the relative clinical and cost-effectiveness of ETA and UGFS for the treatment of primary GSV VV.

Furthermore, the available RCTs evaluated only primary GSV disease and did not study the many other patterns of VV disease seen in everyday clinical practice; and only Rasmussen allowed the inclusion of GSV recurrence within specified parameters. Only Brittenden's supplementary table specified numbers of patients excluded due to technically unsuitable veins for ETA (8.5% of approached patients, although some patients may have also been excluded for technical unsuitability under the title 'vein-related – no further information,' 179 patients).

However, we suggest that the available randomised data do allow a number of observations to be made:

1. All of the endovenous modalities evaluated are extremely safe being associated with a low complication rate and little significant morbidity.^{21,22}
2. All of the RCTs demonstrated that all of the treatments evaluated led to a statistically significant and clinically important improvement in the symptoms and signs of VV disease.
3. Technical failure is fairly consistently reported to be higher after UGFS than with ETA although closure rates after ETA in RCTs do not match the very high rates reported in other studies.^{23–26}
4. Differences in technical success did not relate to differences in clinical (patient reported) outcomes in any of the RCTs and the value of 'technical success' as a useful end-point is questionable.
5. RFA is a highly standardised technique with currently a single device dominating the market.
6. However, this is not the case with EVLA where a large number of different laser technologies, that may have important differences, are currently available.
7. For the purposes of their recommendations, in 2012–2013 NICE decided to consider all ETA techniques together. While, at the time, that was justified on the basis of the available data, technology continues to develop rapidly in this field. As such, it is likely that going forward there will be

outcome heterogeneity with different manufacturers' products.^{21,27}

8. UGFS is an even more heterogeneous treatment modality than ETA with many variables such as the numbers and siting of cannulas, chemical nature, strength and volume of sclerosant used, method of foam preparation, post-procedure compression regime and strategy for re-treatment and aspiration likely to have a major impact on outcomes.
9. The available RCTs have been criticised for using UGFS techniques that would not now be accepted as 'standard of care' but, as noted above, that is a criticism that might also be levelled in terms of the ETA technologies evaluated.^{28–33}
10. Although there is a growing consensus that patient-reported (subjective) outcomes measures (PROMs) are more important than technical (duplex) or physician-reported (objective) outcomes, currently available PROMs tools are imperfect and may miss important (to the patient) differences between different treatments,^{16–19} such as recovery time and time off work.
11. Although due to differences in methods for estimating treatment costs it is difficult to draw any conclusions, it seems likely that local anaesthetic treatment will be more cost-effective than treatment performed under general anaesthesia.
12. Only Brittenden's group calculated QALYs – finding that EVLA had a slightly higher QALYs score than UGFS at five years;²⁰ however, this score was extrapolated from six month follow-up data.
13. All of the RCTs reported UGFS to be less expensive than ETA and give the lack of any difference in clinical outcomes (QoL) it is reasonable to suggest that UGFS will be the more cost-effective option in most patients in most healthcare settings, although this will require more data from long-term follow-up of patients included within these studies to accurately confirm.

Conclusion

All endovenous methods appear to have a role in the treatment of VV. In terms of patient-reported quality of life (QoL), improvement is seen in all groups with no statistical difference. Anatomical success measured with duplex ultrasonography is improved with ETA treatments compared to UGFS, but this may be because of lower technical expertise in a treatment that is more reliant on experience than ETA methods. UGFS requires meticulous technique to provide optimal outcomes with arguably more consideration to treatment tactics than required for ETA methods.

UGFS is also more flexible in its ability to treat recurrence or particularly tortuous VVs. There appears to be a significant cost advantage to UGFS over EVLA and RFA, even if further treatment sessions are required. Although further work is required to optimise UGFS technique to maximise anatomical success and minimise retreatment, the present level 1 evidence base shows it is likely that there is no significant difference in clinically important outcomes between UGFS and ETA. As such strict adherence to the treatment hierarchy recommended by NICE seems unjustified.

Declaration of Conflicting Interests

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